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Review article

Tumor-associated macrophages in skin: How to treat their heterogeneity and plasticity

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ABSTRACT

Immunosuppressive tumor-associated macrophages (TAMs) promote an immunosuppressive environment in the tumor-bearing host, together with regulatory T cells (Tregs). TAMs compose cancer stroma in skin cancers including melanomas and non-melanomas. The majority of tumor-associated macrophages (TAMs) are alternatively activated M2 macrophages that favor tumor development, and they comprise one of the main populations of inflammatory cells in skin cancers. On the other hand, TAMs could be modulated into M1-type macrophages that suppress tumor growth by stimulating and recruiting Th1 and effector cells in the tumor sites. Therefore, TAMs are a target for immunotherapy in various cancers. In this review, we discuss the definition and suppressive mechanisms of TAMs, as well as their biological activities in tumor-bearing hosts to assess potential therapeutic strategies.

Contents

1. Introduction

Immunosuppressive tumor-associated macrophages (TAMs) promote an immunosuppressive microenvironment in the tumor-bearing host, together with regulatory T cells (Tregs) [1]. In dermatological fields, TAMs compose cancer stroma in various skin cancers, including melanoma [2,3], squamous cell carcinoma (SCC) [4,5], extramammary Paget's disease (EMPD) [6,7], and mycosis fungoides (MF) [8,9], and they promote an immunosuppressive tumor microenvironment [1–3,6,9,10]. Since the tumor microenvironment tends to be M-CSF rich, IL-4 rich, and M2 polarized [1,11–14], the majority of TAMs are alternatively activated M2 macrophages that favor tumor development [1,12] and comprise one of the main populations of inflammatory cells in skin cancers [1,10]. On the other hand, TAMs could be modulated into M1-type macrophages to suppress tumor growth by stimulating and

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recruiting Th1 and effector cells in the tumor sites [3]. Therefore, TAMs have been considered as a target for immunotherapy in various cancers [10]. In this review, we discuss the definition and suppressive mechanisms of TAMs, as well as their biological activities in tumor-bearing hosts to assess potential therapeutic strategies.

2. Significance of macrophage heterogeneity in tumors

TAMs are characterized by their heterogeneity and plasticity [1,11,15]. TAMs could be functionally reprogrammed to polarized phenotypes by exposure to cancer-related factors, stromal factors or infection [7,8,10–12]. For example, microbial stimuli such as bacterial infection as well as the administration of type I or type II interferon (IFN) could induce classically activated M1 macrophages [3,10,11,16]. In contrast, M-CSF, IL-4 and IL-13 produced by tumor cells could induce alternative activated M2 macrophages [11,12,17]. Gordon and Martinez [17] described the development of monocytes into mature and fully activated macrophages as three successive stages, which are consistent with the heterogeneity and plasticity of TAMs (Fig. 1). In the first phase, in vitro experiments suggest that the balance of M-CSF and GM-CSF is primarily responsible for determining the phenotype of the mature macrophage. In the second phase, monocytes are primed with several cytokines, such as IFN-γ, IL-4, and IL-13. During the third phase of activation, macrophages reach a mature functional phenotype in response to microbial and opsonic stimuli, such as antibody complexes [17]. Notably, several recent reports suggest that cancer cells, cancer-specific stromal factors derived from tumor cells or cancer inflammation stimulate TAMs in the local site to maintain the characteristic tumor microenvironment in skin cancer [7,8,18,50]. For example, soluble RANKL derived from Paget cells activates $CD163^{+}CD206^{+}Arginase1^{+}$ M2 macrophages to produce CCL17, leading to the recruitment of Tregs to the tumor microenvironment of extramammary Paget's disease [7]. In another report, Wu et al. [18] found that macrophage-related chemokines and angiogenic factors produced by TAMs, which could be augmented by the stimulation of periostin (POSTN) in the cancer stroma of MF [8], have crucial roles in tumor formation in the lesional skin of MF by using a xenografted human CTCL cell model [18]. In addition, Gehrke et al. [50] reported that metastatic melanoma cells stimulate macrophages to produce IL-1β, suggesting that melanoma cells might induce the accumulation of myeloid-derived suppressor cells (MDSCs) by the stimulation of TAMs in tumor bearing hosts [20]. These studies suggest that the depletion or immunomodulation of TAMs might be beneficial for anti-cancer therapy.

Since TAMs are a heterogeneous population of myeloid cells that consecutively differentiate into matured phenotypes, the assessment of their markers is important to understand the states of TAMs in the cancer stroma. Classically, the phenotypes of M1 macrophages are $IL\text{-}12^{high}$, $IL\text{-}23^{high}$, and $IL\text{-}10^{low}$ with variable capacities to produce inflammatory cytokines, such as IL-1β, IL-6, and TNF, and effector molecules, such as reactive oxygen [12]. On the other hand, M2 macrophages produce low levels of IL-12 and IL-23 and high levels of IL-10, promote resolution of inflammation including angiogenesis and tissue remodeling, and contribute to a Th2 response [10–12]. Cell surface and intracellular markers could also be useful for the differentiation of the polarization of TAMs (Fig. 2). In humans, CD68, CD86, CD169, HLA-DR and CCR7 could be markers for M1-shifted TAMs, whereas CD163, CD204, CD206, PD-L1 and arginase 1 could be markers for M2-shifted TAMs [1,10]. In addition, functional markers for M2-like TAMs have been reported [1]. Among them, a series of chemokines can be used to distinguish the activation stages of TAMs. Taken together, these findings indicate that TAMs could be polarized to both M1 and M2 phenotypes by different stromal factors in each cancer.

3. Tumor-loading activities of TAMs

3.1. TAMs suppress antitumor effects of tumor-infiltrating T cells

Part of the suppressive function of M2-polarized TAMs is mediated by the metabolism of L-arginine. M2-polarized TAMs express high levels of arginase 1, which enhances L-arginine catabolism, causes a shortage of L-arginine in the tumor

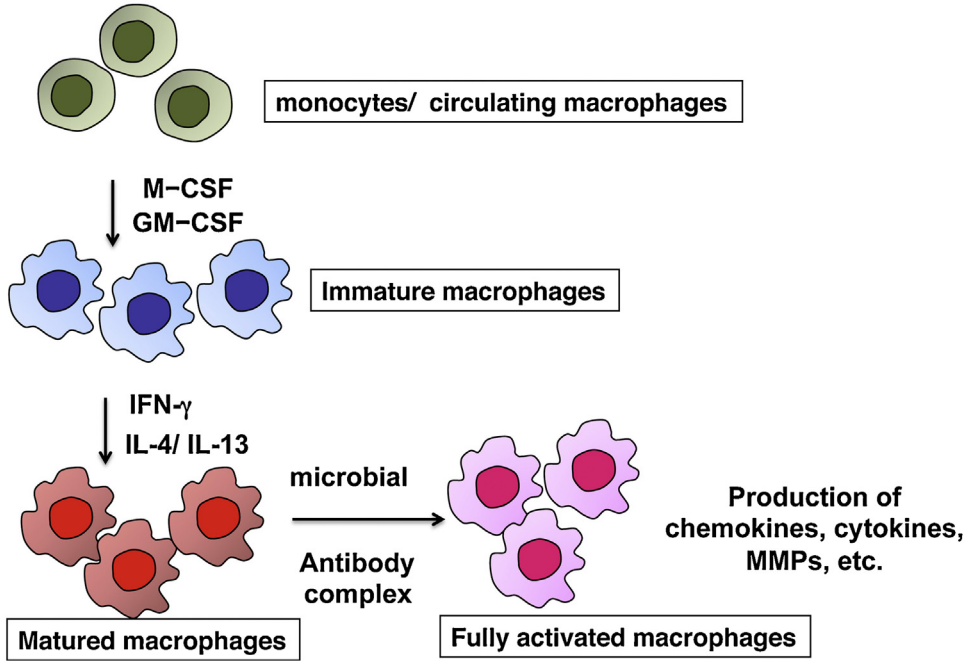

Fig. 1. The heterogeneity and plasticity of TAMs.
The development of monocytes into mature and fully activated macrophages occurs in three successive stages.